BREAKING ADVANCES

2493  Highlights from Recent Cancer Literature

CANCER RESEARCH 75TH ANNIVERSARY COMMENETRIES

2495  The Impact of Nathan Mantel’s “The Detection of Disease Clustering and a Generalized Regression Approach”
Michelle Wynne, Kelley M. Kidwell, and Sofia D. Merajver

2497  PDT: What’s Past is Prologue
Keith A. Cengel, Charles B. Simone II, and Eli Glatstein

REVIEWS

2500  Mitochondrial Sirtuins in Cancer: Emerging Roles and Therapeutic Potential
Jasmine George and Nihal Ahmad

2507  Carcinoma Cell Hyaluronan as a “Portable” Cancerized Prometastatic Microenvironment
Eva A. Turley, David K. Wood, and James B. McCarthy

INTEGRATED SYSTEMS AND TECHNOLOGIES

2513  Elucidation of the Roles of Tumor Integrin β1 in the Extravasation Stage of the Metastasis Cascade
Michelle B. Chen, John M. Lamar, Ran Li, Richard O. Hynes, and Roger D. Kamm
 précis: High spatio-temporal resolution imaging in a novel model of the tumor microenvironment reveals the precise cellular events through which integrin β1 promotes extravasation of tumor cells from the vasculature during the final stage of the metastatic cascade.

MICROENVIRONMENT AND IMMUNOLOGY

2525  TGFβ Signaling in the Pancreatic Tumor Microenvironment Promotes Fibrosis and Immune Evasion to Facilitate Tumorigenesis
Daniel R. Principe, Brian DeCant, Emman Mascariñas, Elizabeth A. Wayne, Andrew M. Diaz, Naomi Akagi, Rosa Hwang, Boris Pasche, David W. Dawson, Deyu Fang, David J. Bentrem, Hidayatullah G. Munshi, Barbara Jung, and Paul J. Grippo
 précis: Targeting the tumor-promoting effects of stromal-derived TGFβ signaling in pancreatic cancer may constitute an applicable strategy in patients no longer benefiting from TGFβ-induced tumor suppression.

2540  Feasibility of Telomerase-Specific Adoptive T-cell Therapy for B-cell Chronic Lymphocytic Leukemia and Solid Malignancies
Sara Sandri, Sara Bobisse, Kelly Mosley, Alessia Lamolinara, Francesco De Sanctis, Federico Boschi, Andrea Sbarbati, Gáulio Fracasso, Giovanna Ferrarini, Rudi W. Hendriks, Chiana Cavallini, Maria Teresa Scupoli, Silvia Santoris, Manuela Iezzi, Michael J. Nishimura, Vincenzo Broni, and Stefano Ugel
 précis: This study exploited the tumor-specific expression of human telomerase to generate a high avidity T-cell receptor for adoptive cell therapy of a B-cell leukemia, illustrating its potency and safety in a preclinical model.

2552  CSF1 Overexpression Promotes High-Grade Glioma Formation without Impacting the Polarization Status of Glioma-Associated Microglia and Macrophages
Ishani De, Megan D. Steffen, Paul A. Clark, Clayton J. Patros, Emily Sokn, Stephanie M. Bishop, Suzanne Litscher, Vilena I. Maklakova, John S. Kuo, Fausto J. Rodriguez, and Lara S. Collier
 précis: CSF1 mediates oncogenic effects during gliomagenesis by acting in the tumor microenvironment, but its actions do not appear to be mediated by altering the polarization state of glioma-associated macrophages/microglia as expected.

2561  IL15 Agonists Overcome the Immunosuppressive Effects of MEK Inhibitors
Michael J. Allegrezza, Melanie R. Rutkowski, Tom L. Stephen, Nikolaos Svoronos, Amelia J. Tesone, Alfredo Perales-Puchalt, Jenny M. Nguyen, Fahmida Sarmin, Mee R. Sheen, Emily K. Jeng, Julia Tchou, Hing C. Wong, Steven N. Fiering, and Jose R. Conejo-Garcia
 précis: Small molecules used as anticancer-targeted therapies have significant immunosuppressive effects by interfering with signaling pathways that are critical for T-cell responses, but in cases of MEK inhibitors, these effects can be effectively rescued by IL15 superagonists available for clinical administration.
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2573</td>
<td>Stromal-Based Signatures for the Classification of Gastric Cancer</td>
<td>Mark T. Uhlik, Jianguang Liu, Beverly L. Falcon, Seema Iyer, Julie Stewart, Hilal Celikkaya, Marguerita O'Mahony,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Christopher Sevinskey, Christina Lowes, Larry Douglass, Cynthia Jeffries, Diane Bodenmiller,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sudhakar Chinthapapalli, Anthony Fischl, Damien Gerald, Qi Xue, Jee-yun Lee, Alberto Santamaria-Pang,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yousef Al-Kofahi, Yupxia Sui, Keyur Desai, Thompson Doman, Amit Aggarwal, Julia H. Carter, Bronislaw Pytowski,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shou-ching Jaminet, Fiona Ginty, Anjaz Nasir, Janice A. Nagy, Harold F. Dvorak, and Laura E. Benjamin</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Précis:</strong> Classifying gastric cancer based on stromal gene expression signatures highlights a new approach to identify potential biomarkers to predict patient responses to antiangiogenesis agents and immunotherapy.</td>
</tr>
</tbody>
</table>

**MOLECULAR AND CELLULAR PATHOLOGY**

| 2587 | The Prosurvival IKK-Related Kinase IKKe Integrates LPS and IL17A Signaling Cascades to Promote Wnt-Dependent Tumor Development in the Intestine | Serkan Ismail Göktuna, Kateryna Shostak, Tieu-Lan Chau, Lucas C. Heukamp, Benoit Hennuy, Hong-Quan Duong, Aurelie Ladang, Pierre Close, Iva Klevernik, Fabrice Olivier, Alexandra Florin, Grégory Ehx, Frédéric Baron, Maud Vandereyken, Souad Rahmouni, Lars Vereecke, Geert van Loo, Reinhard Büttner, Florian R. Greten, and Alain Chariot |
|      |                                                                      | **Précis:** Wnt-driven intestinal tumors initially developing in the absence of inflammatory cues appear to trigger proinflammatory signaling cascades that also promote the establishment of a proinflammatory environment supportive of tumor growth. |

| 2600 | Synergistic Activation of ERs by Estrogen and Prolactin in Breast Cancer Cells Requires Tyrosyl Phosphorylation of PAK1 | Peter Oladimeji, Rebekah Skerl, Courtney Rusch, and Maria Diakonova |
|      |                                                                      | **Précis:** These findings illustrate a mechanism of drug resistance in breast cancer and reveals a potential strategy to improve therapeutic responses. |

| 2612 | Genomic Loss of DUSP4 Contributes to the Progression of Intraepithelial Neoplasm of Pancreas to Invasive Carcinoma | Naoki Hijiya, Yoshiyuki Tsukamoto, Chisato Nakada, Lam Tung Nguyen, Tomoki Kai, Keiko Matsuura, Kohei Shihata, Masafumi Inomata, Tomohisa Uehida, Akinori Tokunaga, Kohei Amada, Kuniaki Shirao, Yasunari Yamada, Hiromu Mori, Ichiro Takeuchi, Masao Seto, Masahiro Aoki, Mutsuhiro Takekawa, and Masatsugu Moriyama |
|      |                                                                      | **Précis:** Loss of chromosome 8p occurring early in development of pancreatic cancer can be compensated for therapeutic inhibition of ERK signaling, a potentially useful strategy to prevent the progression of invasive disease. |

| 2626 | The Ribonucleic Complex HuR-MALAT1 Represses CD133 Expression and Suppresses Epithelial–Mesenchymal Transition in Breast Cancer | Elisa Latorre, Stephana Carelli, Ivan Raimondi, Vito D'Agostino, Ilaria Castiglioni, Chiara Zucal, Giacomena Moro, Andrea Luciani, Giorgio Ghilardi, Eleonora Monti, Alberto Inga, Anna Maria Di Giulio, Alfredo Gorio, and Alessandro Provenzani |
|      |                                                                      | **Précis:** The mechanism underlying derepression of a critical metastasis-inducing gene in breast cancer appears to involve a regulatory complex that requires the presence of a long noncoding RNA component to suppress EMT-like traits. |

| 2637 | An Epigenetic Reprogramming Strategy to Resensitize Radioresistant Prostate Cancer Cells | Claudia Peitzsch, Monica Ciojoc, Linda Hein, Ina Kurt, Katrin Mabel, Franziska Trautmann, Barbara Klink, Evelin Schrock, Manfred P. Wirth, Mechthild Krause, Eduard A. Stakhovsky, Genndy D. Telegiev, Vladimir Novotny, Marieta Toma, Michael Muters, Gustavo B. Baretton, Fiona M. Frame, Norman J. Maitland, Michael Baumann, and Anna Dubrovskova |
|      |                                                                      | **Précis:** A preclinical rationale for the investigation of therapeutic strategies combining radiation and epigenetic agents for the treatment of prostate cancer is presented by findings that prostate cancer cells can be forced to respond to therapy by pharmacological rewiring of the epigenome. |

|      |                                                                      | **Précis:** This study describes a mass spectrometry-based method that can readily define the distribution of DNA-protein crosslinks in various tissues, with implications for cancer risk assessment. |
CHEMICAL BIOLOGY

2698 Natural Product Vibsanin A Induces CK2α Drives Lung Cancer Metastasis by Targeting BRMS1 Nuclear Export and Degradation

2675 Rab11-FIP1C Is a Critical Negative Regulator in ErbB2-Mediated Mammary Tumor Progression

2687 CRM1 Inhibition Promotes Cytotoxicity in Ewing Sarcoma Cells by Repressing EWS-FL1–Dependent IGF-1 Signaling

2700 Intracellular Released Payload Influences Potency and Bystander-Killing Effects of Antibody-Drug Conjugates in Preclinical Models

2662 Precis: An effector of small GTPase Rab11 functions as a tumor suppressor in ErbB2-amplified breast cancer, but as an oncogene in other breast tumor subtypes, illustrating the need to understand the context of a conserved signaling pathway in tailoring patient treatments.

2684 Precis: This study identifies an actionable posttranslational regulatory mechanism that blocks metastasis, including possibly in heterogeneous cellular states that are inherent to this advanced disease state.

2686 Precis: These findings provide a strong rationale to reposition GSK3 inhibitors in clinic to enhance a novel differentiation-based therapy for AML treatment.

2720 Precis: These findings provide strong support for HSP70 inhibition as a therapeutic strategy in melanoma, especially as an adjuvant approach for overcoming the resistance to BRAF inhibitors frequently observed in melanoma patients.

2671 Precis: A novel mechanism of action for HSP90 inhibitors involving the suppression of androgen receptor splicing strengthens predictions that these therapeutics may elicit potent clinical responses in advanced prostate cancers.

2678 Precis: A plant-derived factor with potent antileukemia activity may serve as a novel differentiation-inducing agent to treat acute myeloid leukemias that do not respond to all-trans retinoic therapy, a present standard of care.

2683 Precis: These findings offer a preclinical rationale to reposition GSK3 inhibitors in clinic to enhance a novel differentiation-based therapy for AML treatment.
### Table of Contents

**2754**  
Stress Chaperone Mortalin Contributes to Epithelial-to-Mesenchymal Transition and Cancer Metastasis  
Youjin Na, Sunil C. Kaul, Jihoon Ryu, Jung-Sun Lee, Hyo Min Ahn, Zeenia Kaul, Rajkumar S. Kalra, Ling Li, Nashi Widodo, Chae-Ok Yun, and Renu Wadhwa  

Precis: These findings suggest that the aberrant enrichment of a stress chaperone protein in multiple tumor types elicits an EMT-like phenotype and promotes the invasiveness of cancer cells, warranting further investigation as a potentially broad-acting therapeutic target.

**2766**  
Quantitative Phosphotyrosine Profiling of Patient-Derived Xenografts Identifies Therapeutic Targets in Pediatric Leukemia  

Precis: Phosphotyrosine profiling of patient-derived xenografts may offer an unbiased quantitative approach to define aberrant signaling nodes and identify clinically actionable targets in pediatric leukemias.

**2778**  
The BRCA1-311q Alternative Splice Isoform Bypasses Germline Mutations and Promotes Therapeutic Resistance to PARP Inhibition and Cisplatin  

Precis: Cancer cells generate BRCA splice isoforms to evade the deleterious effects of germline mutations, producing altered proteins capable of promoting therapeutic resistance and thereby targets for resensitization.

### TUMOR AND STEM CELL BIOLOGY

**2791**  
Heparanase 2 Attenuates Head and Neck Tumor Vascularity and Growth  
Miriam Gross-Cohen, Sari Feld, Ilana Dowek, Gera Neufeld, Peleg Hasson, Gil Arvatz, Uri Barash, Inna Naroditsky, Neta Ilan, and Israel Vlodavsky  

Precis: These findings show how overexpression of an isoform of heparanase, Hpa2, inhibits the malignant growth of head and neck cancers, which are rising in incidence.

**2802**  
JPO2/CDCA7L and LEDGF/p75 Are Novel Mediators of PI3K/AKT Signaling and Aggressive Phenotypes in Medulloblastoma  
Tiffany Sin Yu Chan, Cynthia Hawkins, Jonathan R. Krieger, C. Jane McGlade, and Annie Huang  

Precis: Studies identify a novel complex interacting with Myc and Akt kinase as a critical mediator of metastatic behavior in medulloblastoma, with potential implications as a novel point for therapeutic intervention in this type of brain cancer.

**2813**  
MIF Maintains the Tumorigenic Capacity of Brain Tumor–Initiating Cells by Directly Inhibiting p53  
Raita Fukaya, Shigeiki Ohta, Tomonori Yaguchi, Yumi Matsuzaki, Iiji Sugihara, Hideyuki Okano, Hideyuki Saya, Yutaka Kawakami, Takeshi Kawase, Kazunari Yoshida, and Masahiro Toda  

Precis: These findings suggest that a macrophage-secreted factor regulates the formation of tumor-initiating cells in brain cancer by directing binding p53, shedding light on how these important drivers of malignancy are formed.

**2824**  
Analysis of Liver Tumor-Prone Mouse Models of the Hippo Kinase Scaffold Proteins RASSF1A and SAV1  
Xiaoying Zhang, Cai Guo, Xiwei Wu, Arthur X. Li, Limin Liu, Walter Tsark, Reinhard Dammann, Hui Shen, Steven L. Vonderfecht, and Gerd P. Pleifer  

Precis: Liver tumor susceptibility of mouse models in which the Hippo kinase scaffold proteins RASSF1A and SAV1 were deleted suggest a more prominent role of SAV1 as a tumor suppressor in the mouse, which cannot easily be extrapolated to human HCC.

**2836**  
Bap1 Is a Bona Fide Tumor Suppressor: Genetic Evidence from Mouse Models Carrying Heterozygous Germline Bap1 Mutations  
Yuvraj Kadariya, Mitchell Cheung, Jinfei Xu, Jiaming Pei, Eleonora Sementino, Craig W. Menges, Kathy Q. Cai, Frank J. Rauscher, Andres J. Klein-Szanto, and Joseph R. Testa  

Precis: Studies in mouse genetic models offer proof of concept for the suggested tumor suppressor function for BAP1, a gene that when mutated, confers a risk of several tumors, including asbestos-induced mesothelioma.
**CORRECTIONS**

2845 Correction: Grapefruit-Derived Nanovectors Use an Activated Leukocyte Trafficking Pathway to Deliver Therapeutic Agents to Inflammatory Tumor Sites

2846 Correction: Radiation-Induced Loss of Salivary Gland Function Is Driven by Cellular Senescence and Prevented by IL6 Modulation

---

**ABOUT THE COVER**

Individuals harboring inherited heterozygous mutations of the \textit{BAP1} gene are predisposed to a spectrum of neoplasms, including malignant mesothelioma. Using genetically engineered mouse models, it was found that inactivating germline \textit{Bap1} mutations behave as potent cancer susceptibility alleles, giving rise to a variety of malignant tumor types, including occasional mesotheliomas. However, high penetrance of mesothelioma in \textit{Bap1}-mutant mice required exposure to asbestos. The image depicts hematoxylin and eosin staining of a spontaneous malignant mesothelioma invading the pancreas of mouse with a germline \textit{Bap1} mutation. For details, see article by Kadariya and colleagues on page 2836.
Cancer Research

76 (9)


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/76/9

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/76/9. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.